Monthly EAP community Q&A webinar

October 10, 2024

Healey & AMG Center
Sean M. Healey & AMG Center for ALS
at Massachusetts General Hospital

Massachusetts General Hospital
Founding Member, Mass General Brigham
Neurological Clinical Research Institute

Presenters

Multi-PI, Healey Center for ALS at MGH

- Suma Babu, MBBS, MPH
  - Assistant Professor of Neurology, Harvard Medical School
  - Co-Director, Neurological Clinical Research Institute, MGH

Prilenia Therapeutics

- Michael R Hayden, MBChB, PhD, FRCPC
  - CEO Prilenia Therapeutics
  - Killam Professor UBC

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Agenda

- Introduction to Pridopidine
- Act for ALS and impact on Pridopidine development: how it leads to EAP2
- Pridopidine EAP 2: Overview and updates
- Discussion and Q and A

What is Pridopidine?

Investigational drug in clinical development for **Huntington's Disease and ALS**

Administered orally twice a day (bid) in morning and evening

Binds and specifically activates a receptor called **Sigma-1 receptor (S1R)**

In clinical trials pridopidine showed a **side effect profile similar to placebo**

May potentially decrease rate of decline of function, speech and respiratory function **in ALS**

McGarry et al., J Huntingtons Dis. 2020;9(2):173-184; McGarry et al., J Huntingtons Dis. 2020;9(4):371-380; Darpo et al., . Neurol Ther. 2023 Apr;12(2):597-617; Hayden, M., et al. (2024). AAN Annual Meeting, Denver, CO, USA, American Academy of Neurology; Geva M., et al. (2024) ENCALS, Stockholm, Sweden.

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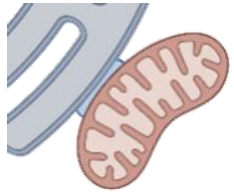
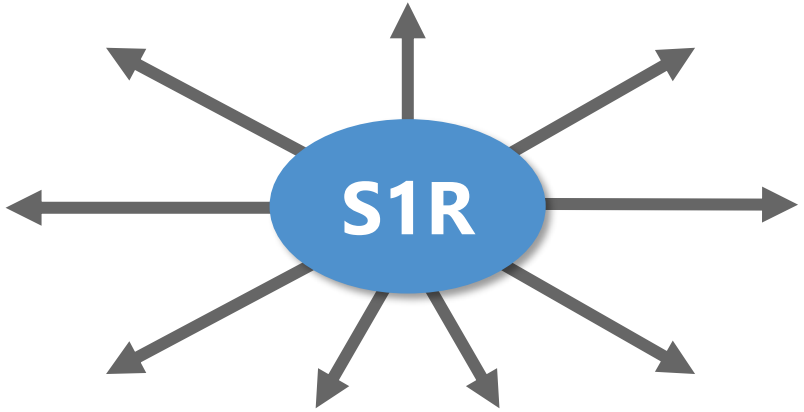
Activation of the Sigma 1-receptor by pridopidine positively influences protective pathways

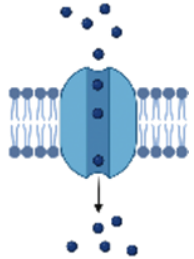
↑ DA release and ↑ interaction with Dopamine D1/2 Receptors and dopaminergic pathways

↑ Mitochondrial-ER Contact

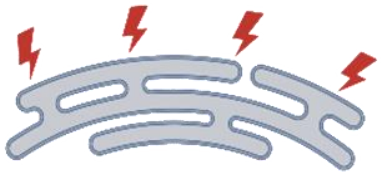




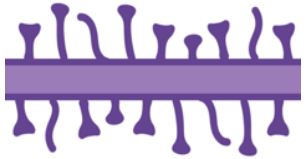
↑ Calcium Homeostasis



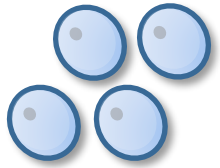
↓ ER Stress



↑ Dendritic Spines

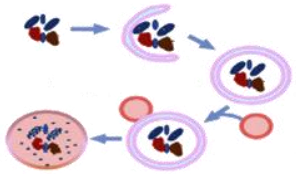


↑ BDNF Transport and Secretion

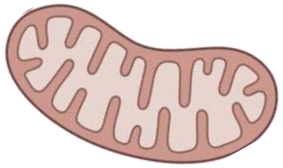


↑ Synaptic Function

↑ Autophagy



↑ Mitochondrial Function



1. Adapted from Aishwarya et al., Front Physiol. 2021; 12:705575, 2. Naia et al, 2021 Neurotherapeutics 18(2):1017-1038, 3. Wang et al., Autophagy. 2022 4:1-26, 4. Ryskamp et al., Neurobiol Dis. 2017; 97:46-59, 5. Geva et al., Hum Mol Genet. 2016 25(18):3975-3987, 6. Francardo et al., Neurotherapeutics. 2019 Apr; 16(2): 465–479 7. Navarro et al, Proceedings of the National Academy of Sciences 2010 107(43):18676-81

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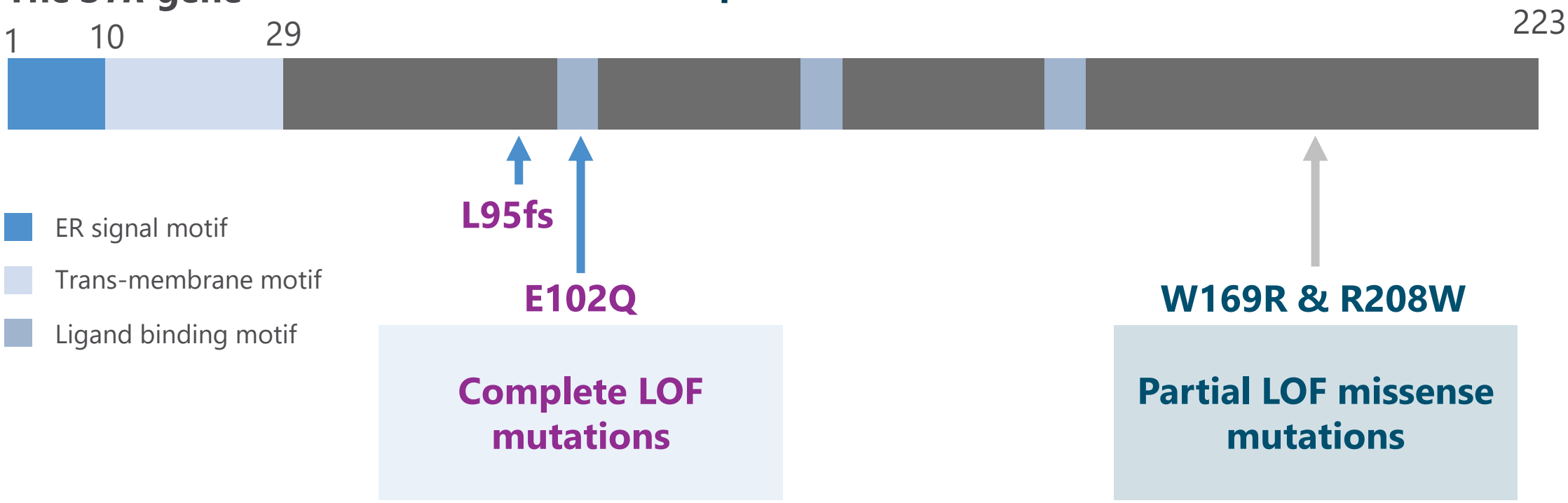
Mutations in the S1R gene cause ALS

Degree of S1R protein loss of function (LOF) determines age of onset

Complete LOF mutations in the *S1R* cause juvenile ALS

Missense mutations with partial loss of function cause adult ALS



Adapted from 1. Al-Saif et al., 2011. Ann Neurol. 2011 Dec;70(6):913-9. 2. Watanabe et al., 2016 EMBO Mol Med. Dec 1;8(12):1421-1437. 3. Izumi et al, 2018 Geriatr Gerontol Int. Oct; 18(10):1519-1520

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Pridopidine has an extensive long-term safety and tolerability profile in clinical trials

Extensive clinical experience

>1,700 participants

in total of

~1,700 patient years

45mg BID exposure

~1,400 participants

in

>1,500 patient years

- Including **long term safety data** (up to 7 years) in HD population
- **Adverse event profile comparable to placebo**

In clinical studies, safety profile is comparable to placebo

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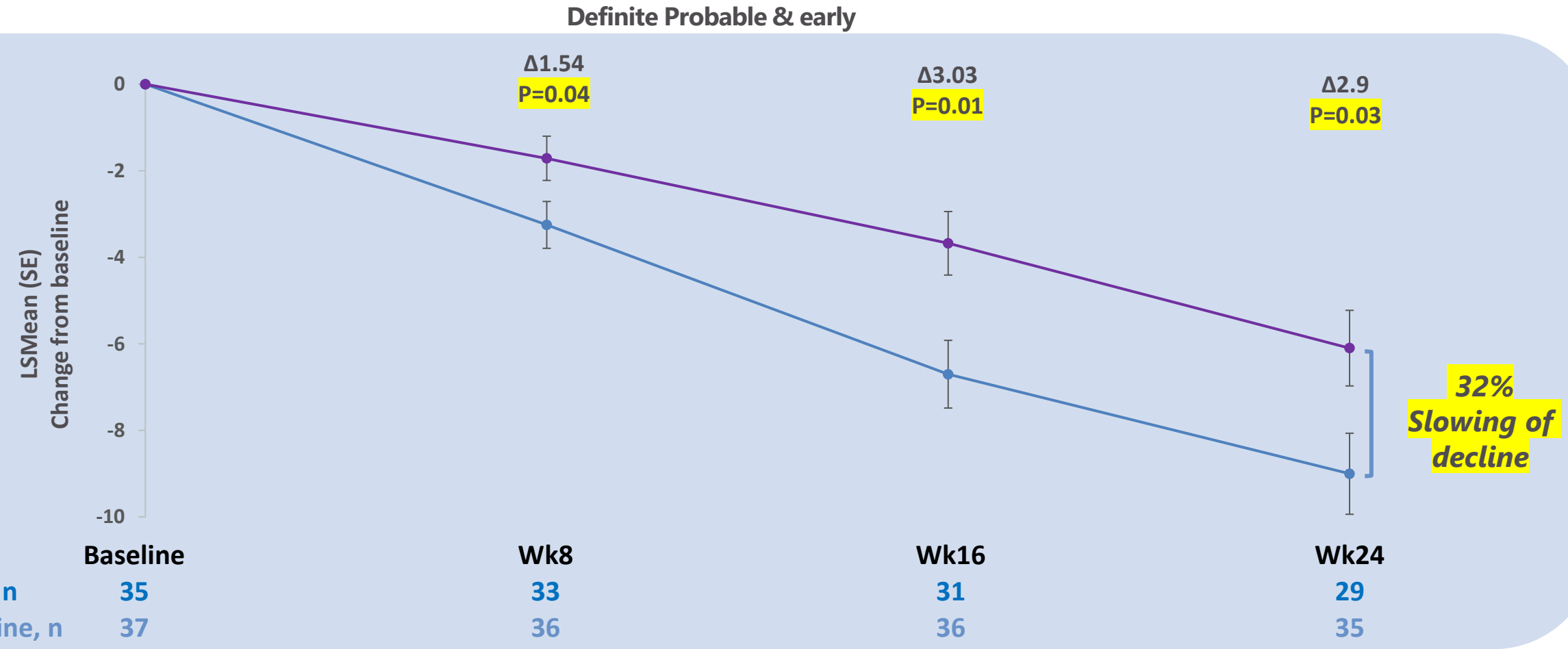
Summary of results Healey Platform study – Regimen D Pridopidine

- In full study population – no benefit seen from pridopidine as compared to placebo
- However, in the pre-defined group of patients with rapidly progressive disease important beneficial effects were seen on function, speech, respiratory function and quality of life

Pridopidine (Regimen D) slows disease progression by 32% at week 24
Definite, Probable & Early (<18 months since onset of symptoms)

LSMean (SE)

Change from baseline in ALSFRS-R



	Baseline	Wk8	Wk16	Wk24
Placebo, n	35	33	31	29
Pridopidine, n	37	36	36	35

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Pridopdine for the treatment of ALS – Results from the Phase 2 Healey ALS Platform Trial. Geva M., et al. (2024) ENCALS, Stockholm, Sweden.

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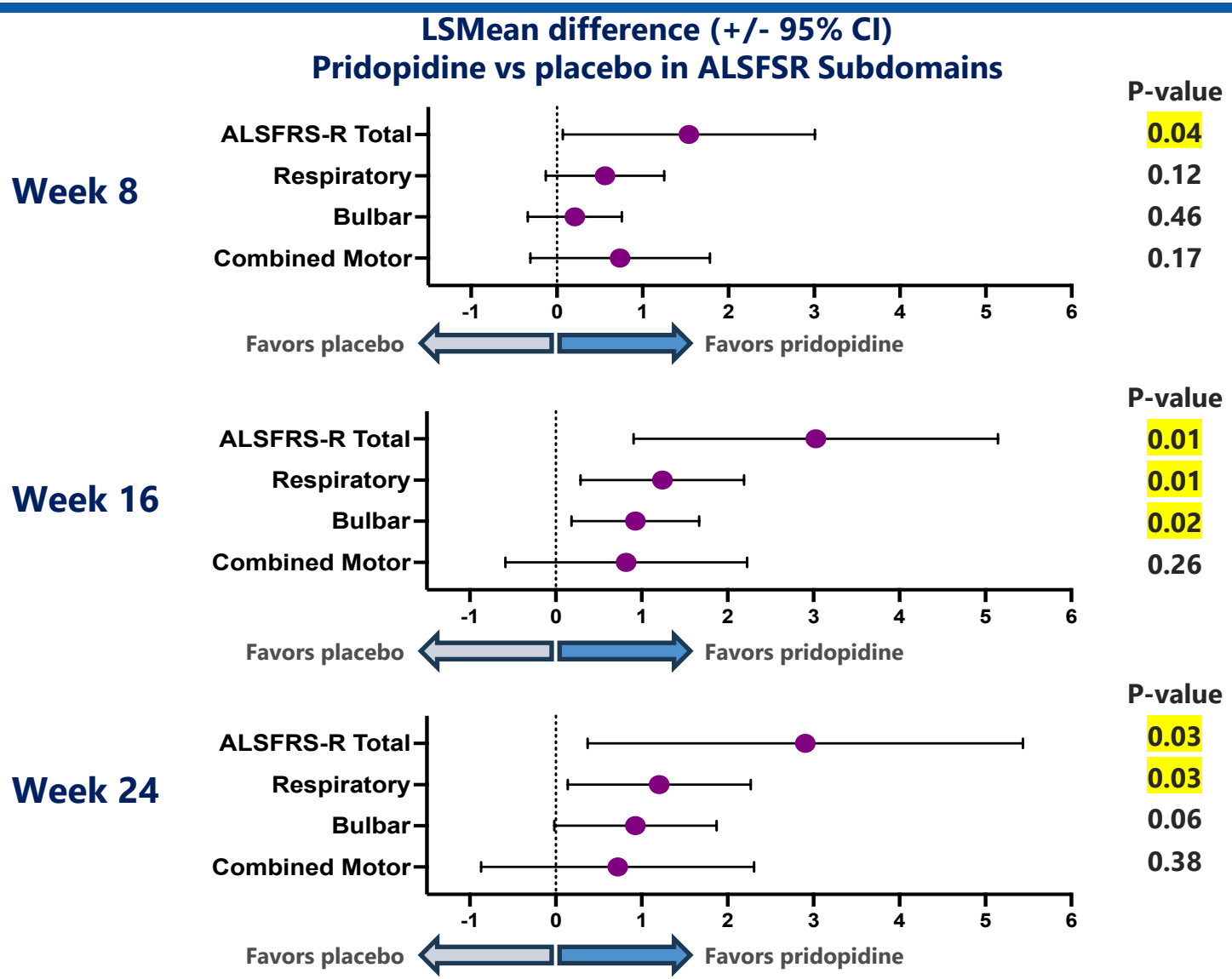
All components of the ALSFRS-R favor pridopidine, at all timepoints
Definite, Probable & Early (<18 months since onset of symptoms)



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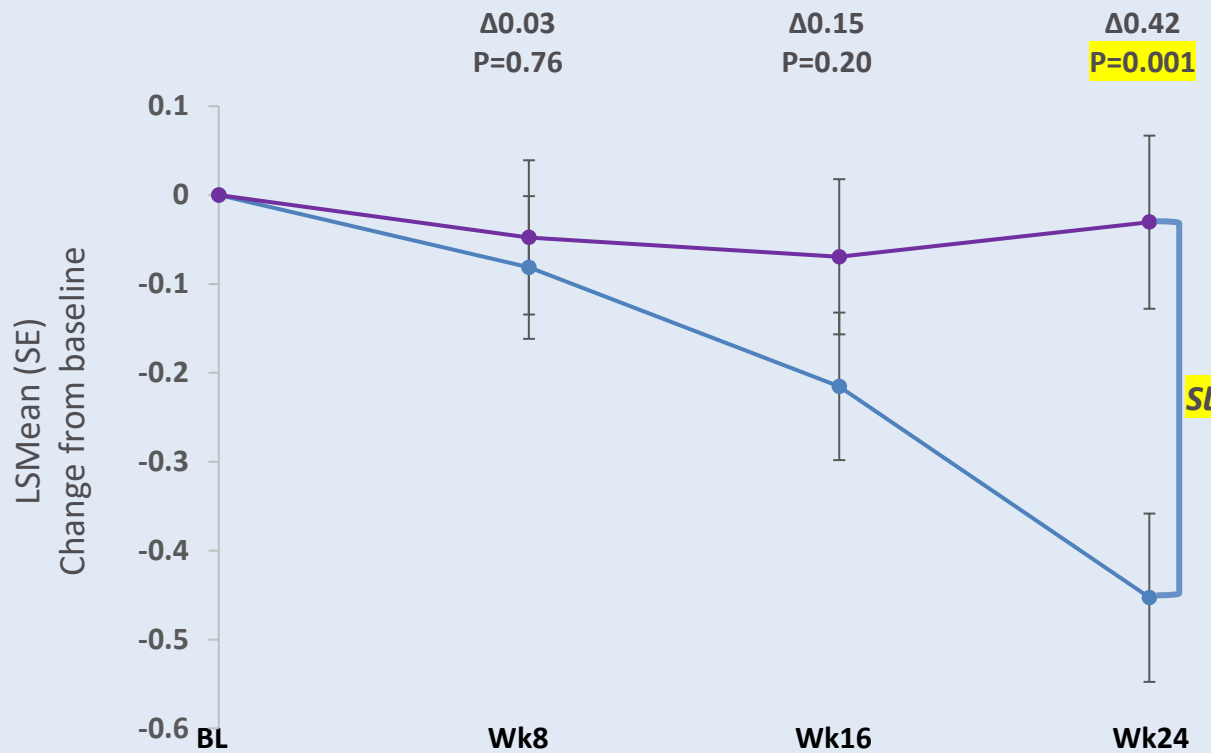
Pridopidine stabilizes Articulation rate (93% slowing of decline) and Speaking rate (65% slowing of decline) up to 24 weeks

Definite, Probable & Early (<18 months since onset of symptoms)

LSMean (SE)

Change from baseline in Articulation rate

Definite, Probable & early

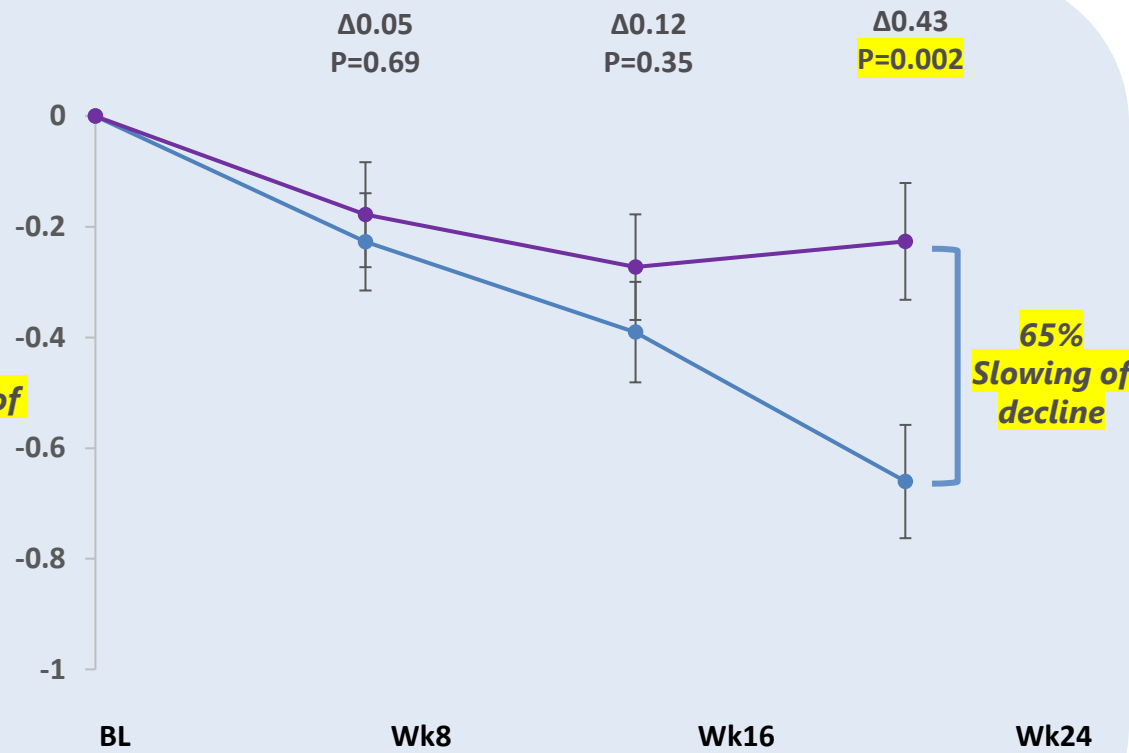


	BL	Wk8	Wk16	Wk24
Placebo, n	31	32	19	22
Pridopidine, n	28	31	30	25

LSMean (SE)

Change from baseline in Speaking rate

Definite, Probable & early



	BL	Wk8	Wk16	Wk24
Placebo, n	31	32	19	22
Pridopidine, n	28	31	30	25

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Prilenia, data on file

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Summary of results Healey Platform study – Regimen D Pridopidine

- In full study population – no benefit seen from pridopidine as compared to placebo
- However, in the pre-defined group of patients with rapidly progressive disease important beneficial effects were seen on function, speech, respiratory function and quality of life
- Encouraging trends were also seen in survival in this group of patients
- No new safety signals were identified

- **These observations inform ongoing planning for Phase III study**

ACT for ALS- A new opportunity to expand access and collect real world data in parallel to clinical trials via EAP

- **ACT for ALS is NIH-funded grant**
- **IND submitted and accepted by the FDA - managed by Healey**
- **Provides expanded access (EAP) to pridopidine for up to 200 ALS patients** (up to 24 months treatment) who are ineligible for clinical trials
- **First participant enrolled** end of March 2024

Healey Center for ALS AT MASSACHUSETTS GENERAL HOSPITAL

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PRESS RELEASE · OCT | 5 | 2023

Sean M. Healey & AMG Center for ALS awarded NIH U01 Grant to support Expanded Access to Pridopidine in Collaboration with Prilenia Therapeutics

NEWS · 5 MINUTE READ · APR | 29 | 2024

The Sean M. Healey & AMG Center for ALS and Prilenia Therapeutics Announce First Participant Enrolled in NIH-Sponsored ACT for ALS Expanded Access Protocol for Pridopidine

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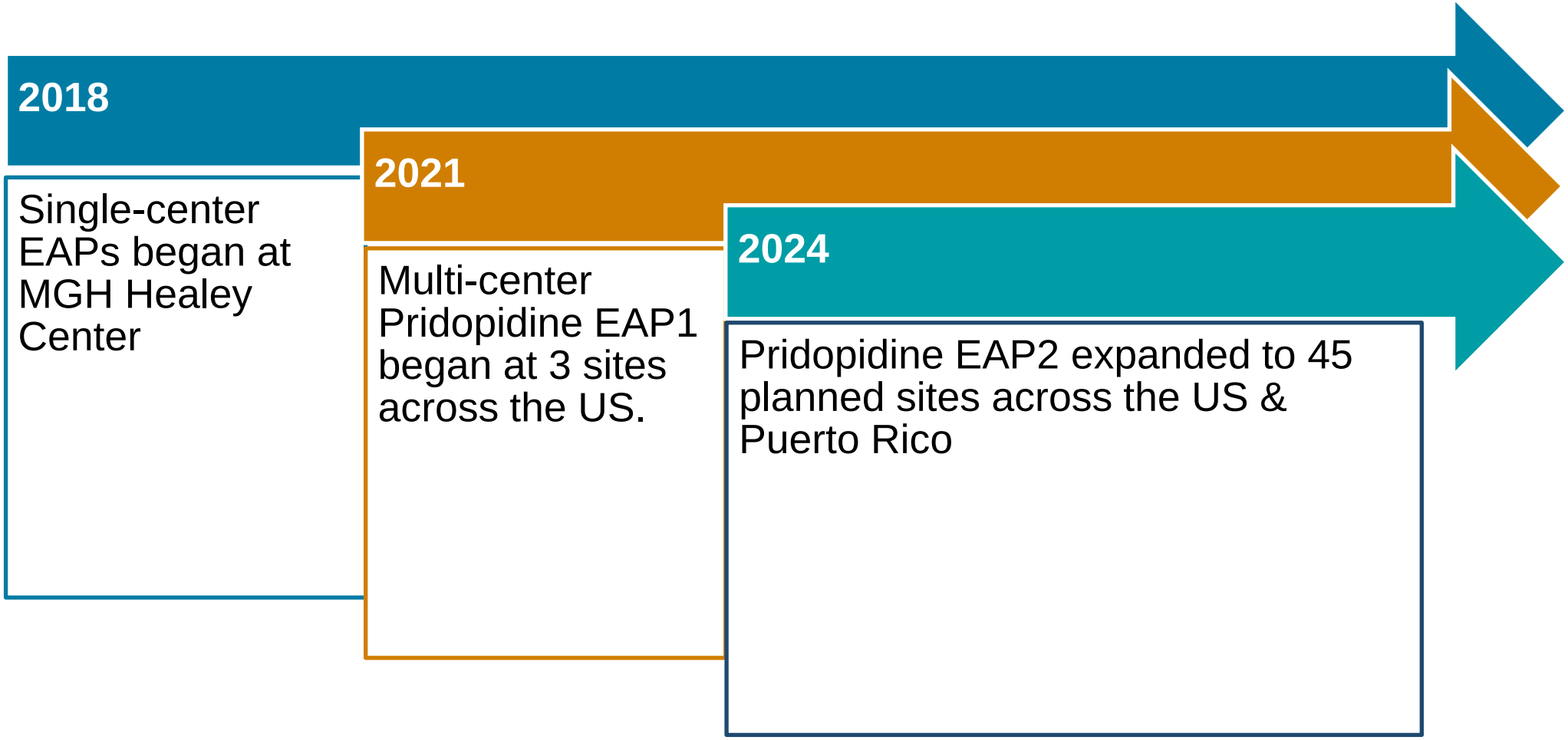
Pridopidine EAP Program Growth at Healey

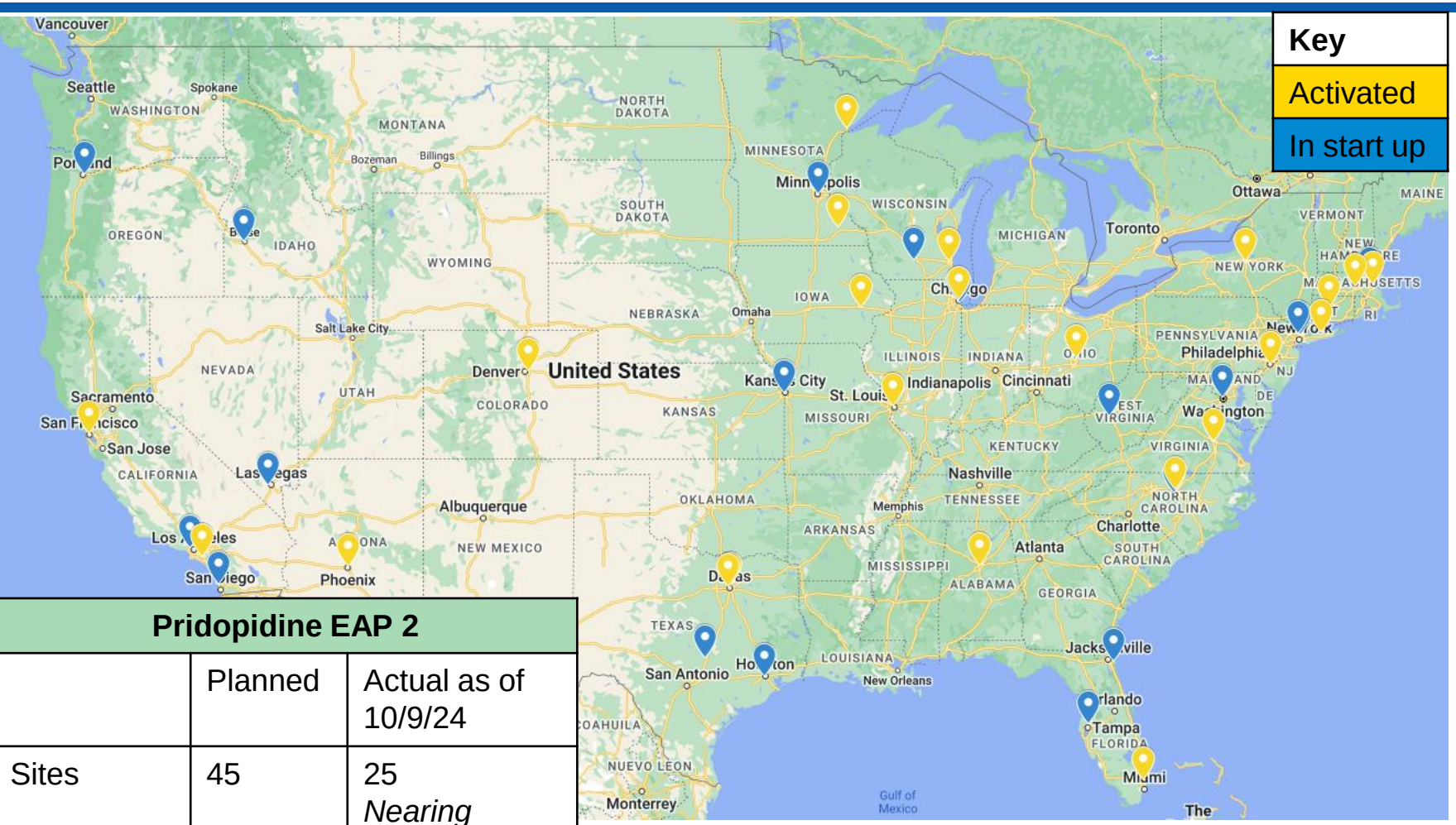


Pridopidine EAP 2

More info: clinicaltrials.gov
NCT06069934

- 45 sites
- Target enrollment: 200 ALS individuals who:
  - do not qualify for clinical trials at the enrolling site and
  - have established care at a specialized ALS center
- Same dose as platform trial: 45 mg twice daily, oral

Pridopidine EAP2: Site Map



Pridopidine EAP 2		
	Planned	Actual as of 10/9/24
Sites	45	25 *Nearing activation: 1*
Participants	200	87 *Screening: 5*

- ✓ Massachusetts General Hospital
- ✓ Texas Neurology
- ✓ California Pacific Medical Center
- ✓ Temple University Hospital
- ✓ Barrow Neurological Institute
- ✓ Hospital for Special Care
- ✓ Washington University School of Medicine
- ✓ University of Iowa
- ✓ Essentia Health
- ✓ Nova Southeastern University
- ✓ Stony Brook University
- ✓ Medical College of Wisconsin
- ✓ Mayo Clinic Rochester
- ✓ SUNY Upstate
- ✓ Virginia Commonwealth University
- ✓ Ohio Health Research Institute
- ✓ University of Alabama at Birmingham
- ✓ Duke University
- ✓ Northwestern University
- ✓ University of California, Irvine
- ✓ UMASS Chan Medical School
- ✓ UT Southwestern
- ✓ University of Colorado
- ✓ University of Puerto Rico
- ✓ Thomas Jefferson University

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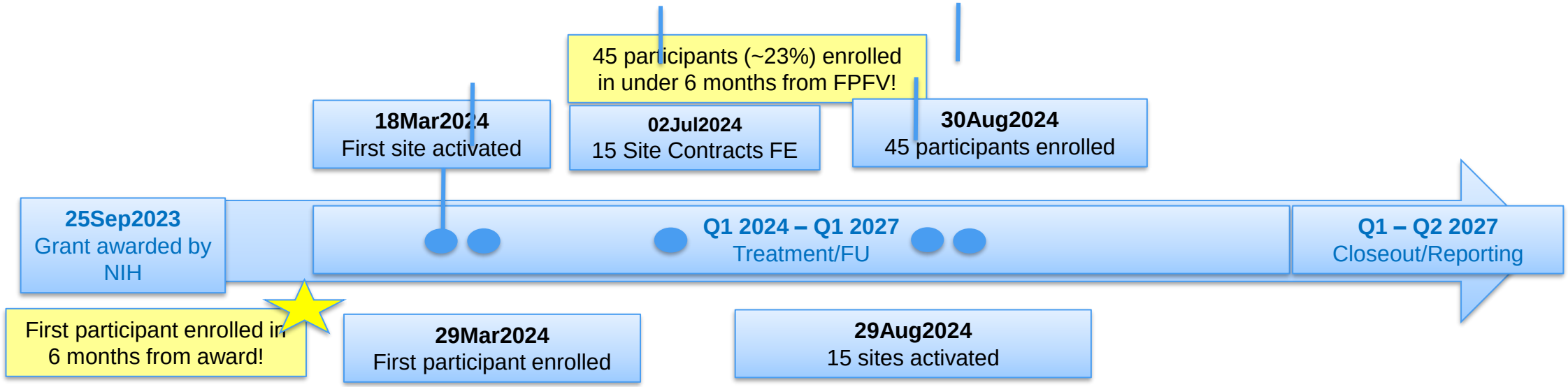
Pridopidine EAP2: Study Updates



Pridopidine EAP2: Study Updates

Study Startup Metrics		
Study Startup Stages	**Pridopidine EAP 2**	**Multi-Site Trials' Average ***
Total Study Start Up Time (Funding to First Participant First Visit)	186 days (6 months)	214 days (7 months)
Funding – IRB Submission	25 days (1 month)	103 days (3 months)
IRB Submission – Approval	40 days (1 month)	60 days (2 months)

Key Factors impacting Startup Timeline:

- Contract negotiations
  - Sponsor, vendors, sites
- Site start up
  - Study staff size and bandwidth (# active projects)
  - Institutional paperwork
  - Site staff training
  - Local and central IRB approvals
  - Newer sites are unfamiliar with differences between EAP and trials

*Cernik, Colin, et al. "Non-cancer clinical trials start-up metrics at an academic medical center: Implications for advancing research." *Contemporary Clinical Trials Communications*, vol. 22, June 2021, p. 100774.

Discussions, Questions, Comments…

THANK YOU!